CLAIMS

1. A combination comprising (a) methotrexate and (b) a non-hepatotoxic DHODH inhibitor, wherein the non-hepatotoxic DHODH inhibitor is chosen from:

2-(3'-ethoxy-3,5-difluorobiphenyl-4-ylamino)nicotinic acid;

2-(3,5-difluoro-3'-methoxybiphenyl-4-ylamino)nicotinic acid;

2-(3'-cyclopropoxy-3,5-difluorobiphenyl-4-ylamino)nicotinic acid;

2-(3,5-difluoro-3'-methoxybiphenyl-4-ylamino)-5-methylnicotinic acid;

or a pharmaceutically acceptable salt or N-oxide thereof.

2. The combination according to claim 1, wherein the non-hepatotoxic DHODH inhibitor is 2-(3'-ethoxy-3,5-difluorobiphenyl-4-ylamino)nicotinic acid or a pharmaceutically acceptable salt or N-oxide thereof.

3. The combination according to claim 1, wherein the non-hepatotoxic DHODH inhibitor is 2-(3,5-difluoro-3'-methoxybiphenyl-4-ylamino)nicotinic acid or a pharmaceutically acceptable salt or N-oxide thereof.

4. The combination according to claim 1, wherein the non-hepatotoxic DHODH inhibitor is 2-(3'-cyclopropoxy-3,5-difluorobiphenyl4-ylamino)nicotinic acid or a pharmaceutically acceptable salt or N-oxide thereof.

5. The combination according to claim 1, wherein the non-hepatotoxic DHODH inhibitor is 2-(3,5-difluoro-3'-methoxybiphenyl-4-ylamino)-5-methylnicotinic acid or a pharmaceutically acceptable salt or N-oxide thereof.

6. The combination according to claim 1, wherein the active ingredients (a) methotrexate, and (b) non-hepatotoxic DHODH inhibitor form part of a single pharmaceutical composition.

7. The combination according to claim 1, further comprising at least one compound (c) chosen from:

(i) Anti-TNF-alpha monoclonal antibodies;

(ii) TNF-alpha Antagonists;

(iii) Calcineurin (PP-2B) Inhibitors/INS Expression Inhibitors;

(iv) IL-1 Receptor Antagonists;
(v) Anti-CD20 monoclonal antibodies;
(vi) p38 Inhibitors;
(vii) NF-kappaB (NFKB) Activation Inhibitors;
(viii) Another dihydrofolate reductase (DHFR) inhibitors;
(ix) Janus kinase (JAK) inhibitors;
(x) MEK inhibitors; and
(xi) Sphingosine-1 phosphate receptor agonists;
(xii) Interferons comprising Interferon beta 1a, and interferons comprising Interferon beta 1 b;
(xiii) Inmunomodulators; and
(xiv) Adenosine aminohydrolase inhibitors.

8. A product comprising (a) methotrexate and (b) a non-hepatotoxic DHODH inhibitor according to claim 1, as a combined preparation for simultaneous, separate or sequential administration.

9. The product according to claim 8, further comprising at least one compound (c) chosen from:
(i) Anti-TNF-alpha monoclonal antibodies;
(ii) TNF-alpha Antagonists;
(iii) Calcineurin (PP-2B) Inhibitors/INS Expression Inhibitors;
(iv) IL-1 Receptor Antagonists;
(vi) p38 Inhibitors;
(vii) NF-kappaB (NFKB) Activation Inhibitors;
(viii) Another dihydrofolate reductase (DHFR) inhibitors;
(ix) Janus kinase (JAK) inhibitors;
(x) MEK inhibitors;
(xv) Interferons comprising Interferon beta 1a, and interferons comprising Interferon beta 1 b;
(xvi) Inmunomodulators; and
(xvii) Adenosine aminohydrolase inhibitors.

10. A kit of parts comprising (a) methotrexate and (b) a non-hepatotoxic DHODH

inhibitor according to claim 1, together with instructions for simultaneous, separate or sequential administration.

11. The kit according to claim 10, further comprising at least one compound (c) chosen from:

(i) Anti-INF-alpha monoclonal antibodies;

(ii) TNF-alpha Antagonists;

(iii) Calcineurin (PP-2B) Inhibitors/INS Expression Inhibitors;

(iv) IL-1 Receptor Antagonists;

(vi) p38 Inhibitors;

(vii) NF-kappaB (NFKB) Activation Inhibitors;

(viii) Another dihydrofolate reductase (DHFR) inhibitors;

(ix) Janus kinase (JAK) inhibitors;

(x) MEK inhibitors;

(xviii) Interferons comprising Interferon beta 1a, and interferons comprising Interferon beta 1b;

(xix) Inmunomodulators; and

(xx) Adenosine aminohydrolase inhibitors.

12. A package comprising (b) a non-hepatotoxic DHODH inhibitor according to claim 1 and (a) methotrexate, for simultaneous, separate or sequential administration.

13. The package according to claim 12, further comprising at least one compound (c) chosen from:

(i) Anti-TNF-alpha monoclonal antibodies;

(ii) TNF-alpha Antagonists;

(iii) Calcineurin (PP-2B) Inhibitors/INS Expression Inhibitors;

(iv) 1L-1 Receptor Antagonists;

(vi) p38 Inhibitors;

(vii) NF-kappaB (NFKB) Activation Inhibitors;

(viii) Another dihydrofolate reductase (DHFR) inhibitors;

(ix) Janus kinase (JAK) inhibitors;

(x) MEK inhibitors;

(xxi) Interferons comprising Interferon beta 1a, and interferons comprising Interferon beta 1b;

(xxii) Inmunomodulators; and

(xxiii) Adenosine aminohydrolase inhibitors.

14. A method for preparing a medicament, comprising: combining (b) a non-hepatotoxic DHODH inhibitor according to claim 1, with (a) methotrexate.

15. Use of (a) methotrexate and (b) a non-hepatotoxic DHODH inhibitor according to the combination of claim 3 in the manufacture of a medicament for treating a human or animal patient suffering from a disease chosen from the group consisting of rheumatoid arthritis, psoriatic arthritis, ankylosing spondilytis, multiple sclerosis, and Wegener's granulomatosis, wherein the disease is ameliorated by inhibition of dihydroorotate dehydrogenase.

16. Use of (a) methotrexate and (b) a non-hepatotoxic DHODH inhibitor according to the combination of claim 3 in the manufacture of a medicament for treating a human or animal patient suffering from a disease chosen from the group consisting of rheumatoid arthritis, psoriatic arthritis, ankylosing spondilytis, multiple sclerosis, and Wegener's granulomatosis, wherein the medicament is effective for reducing hepatotoxicity resulting from liver fibrosis, hepatitis, cirrhosis, or liver cancer of the human or animal patient.

17. The use according to claim 15, wherein the medicament includes (a) methotrexate at a dose of 0.015 to 3 mg/kg/week, and the (b) non-hepatotoxic DHODH inhibitor at a dose of 0.03 to 30 mg/kg/day.

18. The combination of (a) methotrexate and (b) a non-hepatotoxic DHODH inhibitor according to claim 3 for use in treating a human or animal patient suffering from a disease chosen from the group consisting of rheumatoid arthritis, psoriatic arthritis, ankylosing spondilytis, multiple sclerosis, and Wegener's granulomatosis, wherein the disease is ameliorated by inhibition of dihydroorotate dehydrogenase.

19. The combination of (a) methotrexate and (b) a non-hepatotoxic DHODH inhibitor according to claim 3 for use in treating a human or animal patient suffering from a disease chosen from the group consisting of rheumatoid arthritis, psoriatic arthritis, ankylosing spondilytis, multiple sclerosis, and Wegener's granulomatosis,

wherein the combination of claim 3 is effective for reducing hepatotoxicity resulting from liver fibrosis, hepatitis, cirrhosis, or liver cancer of the human or animal patient.

20. The combination according to claim 18, wherein the (a) methotrexate is at a dose of 0.015 to 3 mg/kg/week, and the (b) non-hepatotoxic DHODH inhibitor is at a dose of 0.03 to 30 mg/kg/day.